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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/717,993	11/20/2003	Chi Li Liu	2027.631000	7643

79138 7590 10/21/2008

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EXAMINER	
MEAH, MOHAMMAD Y	
ART UNIT	PAPER NUMBER
1652	
MAIL DATE	DELIVERY MODE
10/21/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/717,993	LIU ET AL.	
	Examiner	Art Unit	
	MD. YOUNUS MEAH	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12-23,129 and 130* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *11* is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

In view of the appeal Brief filed on 07/24/08, PROSECUTION IS HEREBY REOPENED. A new non-final office action is set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patient Examiner (SPE) has approved of reopening prosecution and his signature below.

Following is ground of the rejection of CLAIMS after final appeal brief:

Claims 1-10, 12-23 and 129-130 were examined in the previous action.

Claim Rejection - 35 U.S.C 103a

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made

to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Rejection of claims 1-10, 12-23 and 129-130 under 35 U.S.C. 103(a) by as being obvious over Rajgarhia et al. (US 2004/0029238) in view of Barnett et al. (Yeasts: characterization and identification 2nd edition, Cambridge University press ISBN 052135056, page 20-28 from applicant reference) is withdrawn after finding some of applicants arguments against the use of Barnett et al persuasive. However Rajgarhia et al. (US 2004/0029238) is used for a new 35 U.S.C. 103(a) rejection for claims 1-7, 12-20, 22-23 and 129-130 as explained bellow:

Claims 1-7, 12-20, 22-23 and 129-130 are rejected under 35 U.S.C. 103(a) as being obvious over Rajgarhia et al. (US 2004/0029238) in view of Lee et al. (UK patent 2251864, 1995).

Claims 1 is directed to a method of producing lactic acid, comprising: performing selection on a parent yeast strain that contains an exogenous lactate dehydrogenase gene encoding the amino acid sequence of a lactate dehydrogenase protein of an organism selected from the group consisting *Lactobacillus plantarum, bovine, Lactobacillus casei, Bacillus megaterium, Rhizopus oryzae, or Bacillus stearothermophylus* that is capable of being expressed in the parent yeast strain, to yield an acid-tolerant (AT) yeast strain that is capable of growing in a minimal medium at a lower pH than the parent yeast strain; and culturing in a minimal medium the acid-tolerant (AT) yeast strain, wherein the AT yeast strain produces less than about 1 ppm ethanol, wherein the exogenous lactate dehydrogenase gene is capable of being

expressed in the AT yeast strain, and wherein a protein resulting from the expression of the exogenous lactate dehydrogenase gene has lactate dehydrogenase activity.

Claims 2-4, 12-23 and 129-130 are directed to the method of claim 1 wherein said AT yeast strain is C_2 carbon source independent grows in minimum cultural medium having carbohydrate or glucose as carbon source and/or produce lactic acid at pH 3.5 and as low as pH 2.3. Claims 5-7 are directed to the method of claim 1 wherein said AT yeast strain produces 50 g lactic acid/100 g glucose to upto 70 g/100 g glucose.

Rajgarhia et al. teach various recombinant acid tolerant (AT) yeast strains, i.e., *Kluyvermyces, Candida, etc*, having deleted pyruvate decarboxylase (PDC, example 15) gene (deletion of PDC gene results no ethanol production, pargh 0019 of Rajgarhia et al. and lines 35-45) expressing, through integration to yeast chromosome or through plasmid, various exogenous LDH genes, including from *Rhizopus oryzae, Bacillus megaterium* (paragraph 153). Rajgarhia et al. teach that said yeast strain is capable of growing in minimal medium or C_2 independent medium (pargh. 0115) of cell culture at low pH (below ~2.3, pargh 0024). Rajgarhia et al. also teach said strain could produce upto 90gm lactic acid /100gm of glucose (examples 15-16, table 1 page 13) wherein glucose is only carbon source (see claim 8). However Rajgarhia et al. do not teach a method of selection of most acid tolerant, AT, yeast strain from the parent yeast strain expressing exogenous LDH gene.

It is well known in the art that production of lactic acids in a cultural medium drop the pH of the medium (Lee et al. page 3) and most of the lactic acid producing bacteria do not grow at lower pH (Lee et al. page 1). Yeast cells on the other hand are viable at low pH (Rajgarhia et al. paragraph 005). Lactic acid is an industrially important chemical and to increase the yield of lactic acid, a microbial environment that can tolerate low pH is desired. Selection of microbial cell that grow at most low pH is advantageous for increased production of lactic acid. Rajgarhia et al. teach variants of recombinant yeast strains expressing exogenous LDH genes with the highest specific productivity during the anaerobic phase can be found not only to produce lactic acid faster, but also achieve a higher concentration at a lower pH, than the variants with lower specific productivity (example 15, pargh 195).

Lee et al teach the method of selection of mutant lactobacillus cell which is viable at low pH and produce lactic acid at low pH, wherein parent lactobacillus cell is cultured at various low pH and selection is made for the mutant lactobacillus cell that viable at lower pH than the parent strain (pages 6-7 and claim 9 of lee et al.).

Therefore, one of ordinary skill in prior art would have been **motivated** to use Rajgarhia et al's yeast strains expressing exogenous LDH genes which show the highest specific productivity during the anaerobic phase, produce lactic acid faster and higher concentration at a lower pH (example 15, pargh 195) grow it at lower pH and select the viable yeast cells that produce lactic acid at the lowest pH using the method of Lee et al. One of ordinary skill in the art would have been motivated to do so because recombinant acid tolerant yeast strains expressing exogenous LDH genes is

used for the production of lactic acid, an industrially useful chemical. One of ordinary skill in the art would have been also motivated to select the most acid tolerable yeast strain that produce the highest amount of lactic acid by growing acid tolerant yeast strain and lowering pH and selecting the most viable strain at the lowest pH, because i) use of acid tolerant yeast strains expressing exogenous LDH gene for the efficient production of lactic acid is well known in the art, ii) it is easy to purify lactic acid from yeast media at low pH, iii) yeast strain that produce lactic acid at lowest pH will produce most lactic acid and require least purification step (pargh 0143 of Rajgarhia et al.). As such it would have been obvious to one of ordinary skill in the art to grow Rajgarhia et al's yeast *Kluyvermyces* strains expressing (through integration to yeast chromosome or through plasmid) *Rhizopus oryzae* LDH gene at different media and pHs and make a selection of most acid tolerant (AT) viable strain as taught by Lee et al and use it in the method for the efficient production of lactic acid. The expectation of success is high, because the above cited references define the status of the prior art in the successful method of selection of most acid tolerant yeast strain for the production of lactic acid faster and higher concentration at a lower pH.

Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rajgarhia et al. (US 2004/0029238) in view of Lee et al. (UK patent 2251864, 1995) as applied to claims 1-7, 12-20, 22-23 and 129-130 above, and further in view of House et al (US2003/0228671).

Claim 8 is directed to the method of claim 1 wherein said AT yeast strain produce less than 1 ppm of glycerol.

Rajgarhia et al. teach various recombinant acid tolerant (AT) yeast strains, i.e., *Kluyvermyces, Candida, etc*, having deleted pyruvate decarboxylase (PDC, example 15) gene (deletion of PDC gene results no ethanol production, pargh 0019 of Rajgarhia et al. and lines 35-45) expressing, through integration to yeast chromosome or through plasmid, various exogenous LDH genes, including from *Rhizopus oryzae* (paragraph 153). Lee et al. are described above.

However Rajgarhia et al. do not teach AT yeast strain producing less than 1 ppm of glycerol.

House et al (US2003/0228671) teach method of producing lactic acid using recombinant acid tolerant yeast strains expressing exogenous LDH gene without producing any ethanol or glycerol (page 17, pargh 0209).

As such it would have been obvious to one of ordinary skill in the art to use House et al (US2003/0228671) recombinant acid tolerant yeast strains expressing exogenous LDH gene grow it different media and pHs and make a selection of most AT yeast strain as taught by Lee et al and use it for the efficient production of lactic acid without producing any ethanol or glycerol.

Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rajgarhia et al. (US 2004/0029238) in view of Lee et al. (UK patent 2251864, 1995) as applied to claims 1-7, 12-20, 22-23 and 129-130 above, and further in view of Rajgarhia et al (US2004/0029256).

Claim 21 is directed to the method of claim 1 wherein said AT yeast strain expresses exogenous LDH gene from *lactobacillus plantarum.*

Rajgarhia et al. (US 2004/0029238) teach various recombinant acid tolerant (AT) yeast strains, i.e., *Kluyvermyces, Candida, etc*, having deleted pyruvate decarboxylase (PDC, example 15) gene (deletion of PDC gene results no ethanol production, pargh 0019 of Rajgarhia et al. and lines 35-45) expressing, through integration to yeast chromosome or through plasmid, various exogenous LDH genes, including from *Rhizopus oryzae* (paragraph 153). Lee et al. are described above.

However Rajgarhia et al. (US 2004/0029238) do not teach AT yeast strain expressing exogenous LDH gene from *lactobacillus plantarum.*

Rajgarhia et al (US2004/0029256) teach recombinant acid tolerant yeast strains expressing exogenous LDH gene from *lactobacillus plantarum* (claim 10 of Rajgarhia et al US2004/0029256).

As such, it would have been obvious to one of ordinary skill in the art to use Rajgarhia et al (US2004/0029256) recombinant acid tolerant yeast strains expressing exogenous *lactobacillus plantarum* LDH gene grow it different media and pHs and make a selection of most AT yeast strain as taught by Lee et al and use it for the efficient production of lactic acid.

Claims 9-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rajgarhia et al. (US 2004/0029238) in view of Lee et al. (UK patent 2251864, 1995) as

applied to claims 1-7, 12-20, 22-23 and 129-130 above, and further in view of Porro et al (US 7049108).

Claims 9-10 are directed to the method of claim 1 wherein said AT yeast strain *comprise Saccharomyces or Saccharomyces cerevisiae.*

Rajgarhia et al. (US 2004/0029238) teach various recombinant acid tolerant (AT) yeast strains, i.e., *Kluyvermyces, Candida, etc*, having deleted pyruvate decarboxylase (PDC, example 15) gene (deletion of PDC gene results no ethanol production, pargh 0019 of Rajgarhia et al. and lines 35-45) expressing, through integration to yeast chromosome or through plasmid, various exogenous LDH genes, including from *Bacillus megaterium* (paragraph 153). Lee et al. are described above.

However Rajgarhia et al. (US 2004/0029238) do not teach AT yeast strain comprising *Saccharomyces or Saccharomyces cerevisiae.*

Porro et al teach recombinant *Saccharomyces cerevisiae* yeast strain expressing various exogenous LDH genes including from *Bacillus megaterium,* wherein said yeast strain comprise deleted PDC genes so that it produce no ethanol. However Porro et al. do not teach a method of selection of AT yeast strain from the parent yeast strain expressing exogenous LDH gene.

As such, it would have been obvious to one of ordinary skill in the art to use Porro et al recombinant acid tolerant *Saccharomyces cerevisiae* yeast strain expressing exogenous LDH gene from *Bacillus megaterium* grow it different media and pHs and make a selection of most AT yeast strain as taught by Lee et al and use it for the efficient production of lactic acid.

Conclusion

Claim 11 is allowable and claims 1-10, 12-23 and 129-130 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mohammad Meah whose telephone number is 571-272-1261. The examiner can normally be reached on 8:30-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, NASHAAT T NASHED can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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